

# 1,4-DIOXANE IN PERSONAL CARE & CLEANING PRODUCTS

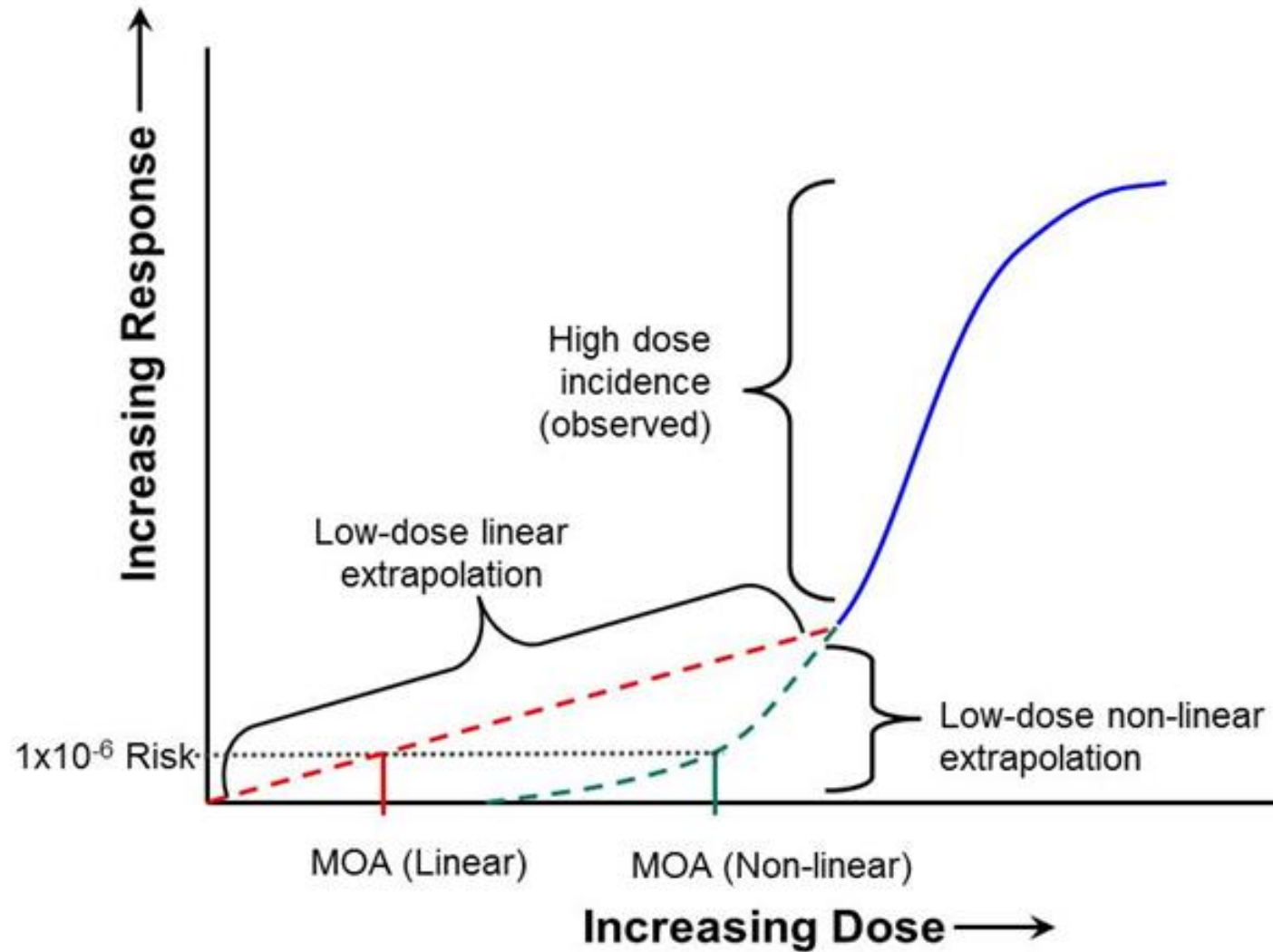
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*June 28, 2019*

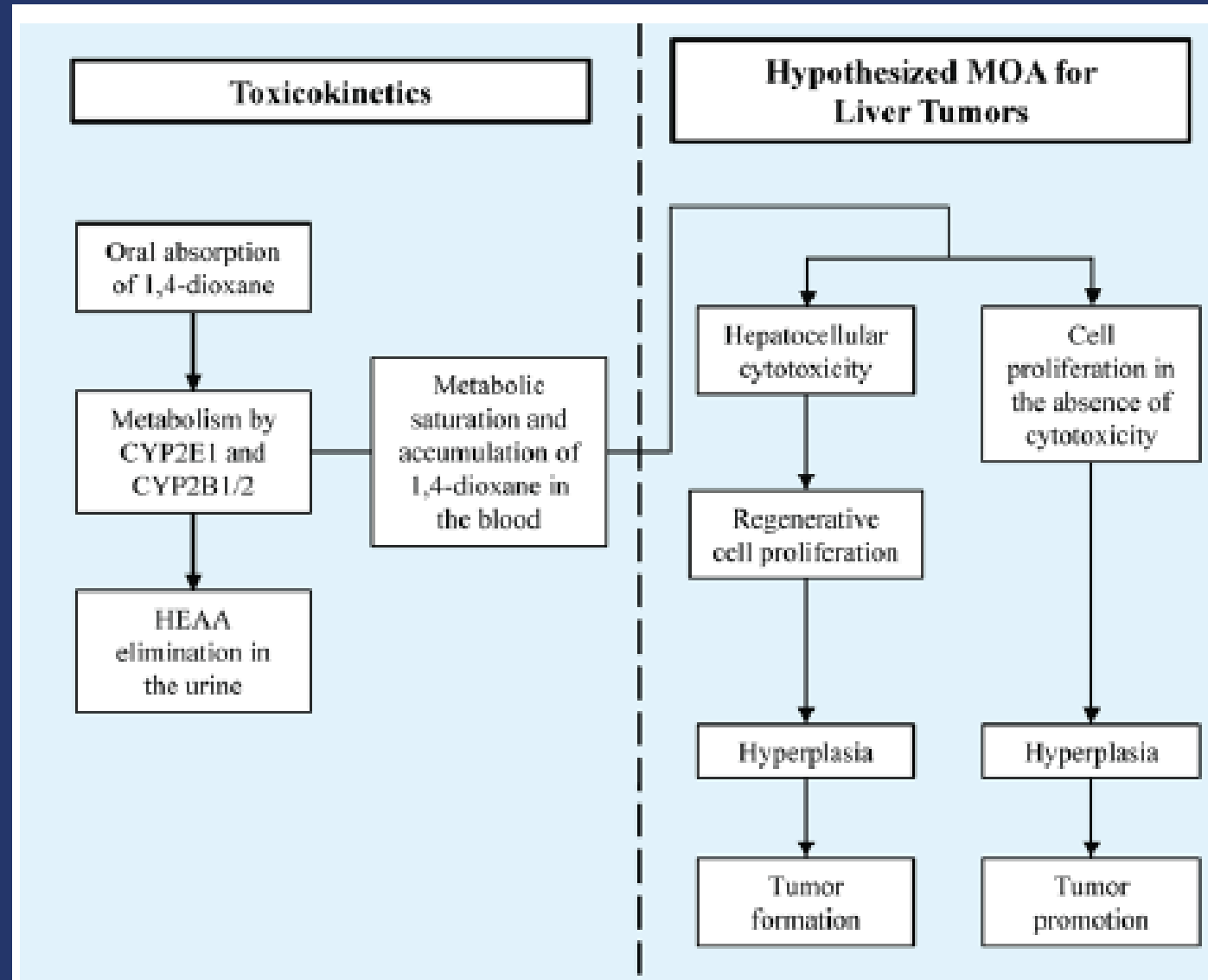
# Previous Conclusions Regarding 1,4-Dioxane Carcinogenicity (~2010-2013)

- 1,4-DX is readily metabolized at lower doses; metabolic saturation occurs at higher doses
- Clear evidence that 1,4-DX and metabolites are not genotoxic
  - Heath Canada, WHO, and EU: tumors form only after metabolic saturation → non-linear (threshold) mode of action (MOA)
- USEPA 2013: there are data supporting a threshold MOA, but --
  - Incomplete evidence that cytotoxicity/proliferation precede tumors
  - Metabolism not completely characterized
  - Lack of evidence of a proliferative response

# Low-Dose Extrapolation (Linear vs Threshold)



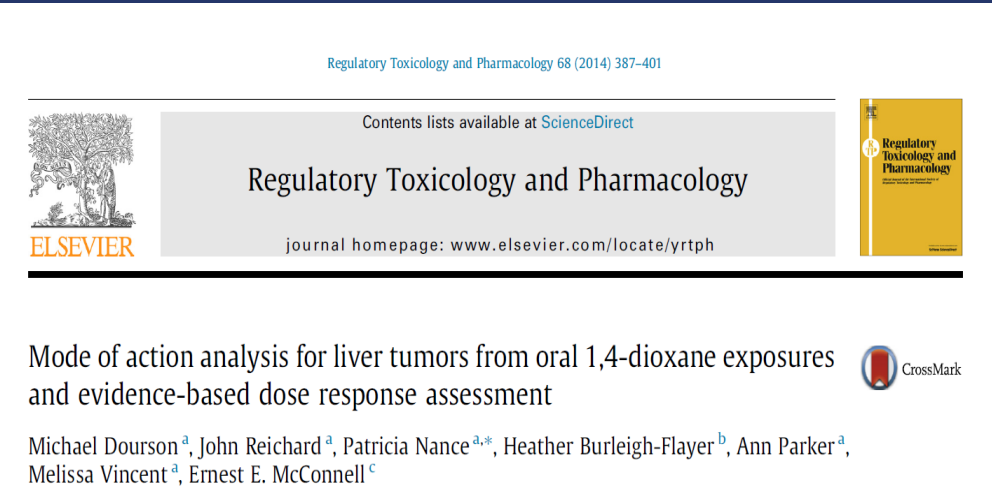
# Key Events in the Regenerative MOA for Carcinogenicity



# Progression to Tumors

*Reg Tox Pharma* 68:387-401  
(2014)

Liver cell toxicity & proliferation  
observed in reanalysis of National  
Cancer Institute (NCI) slides



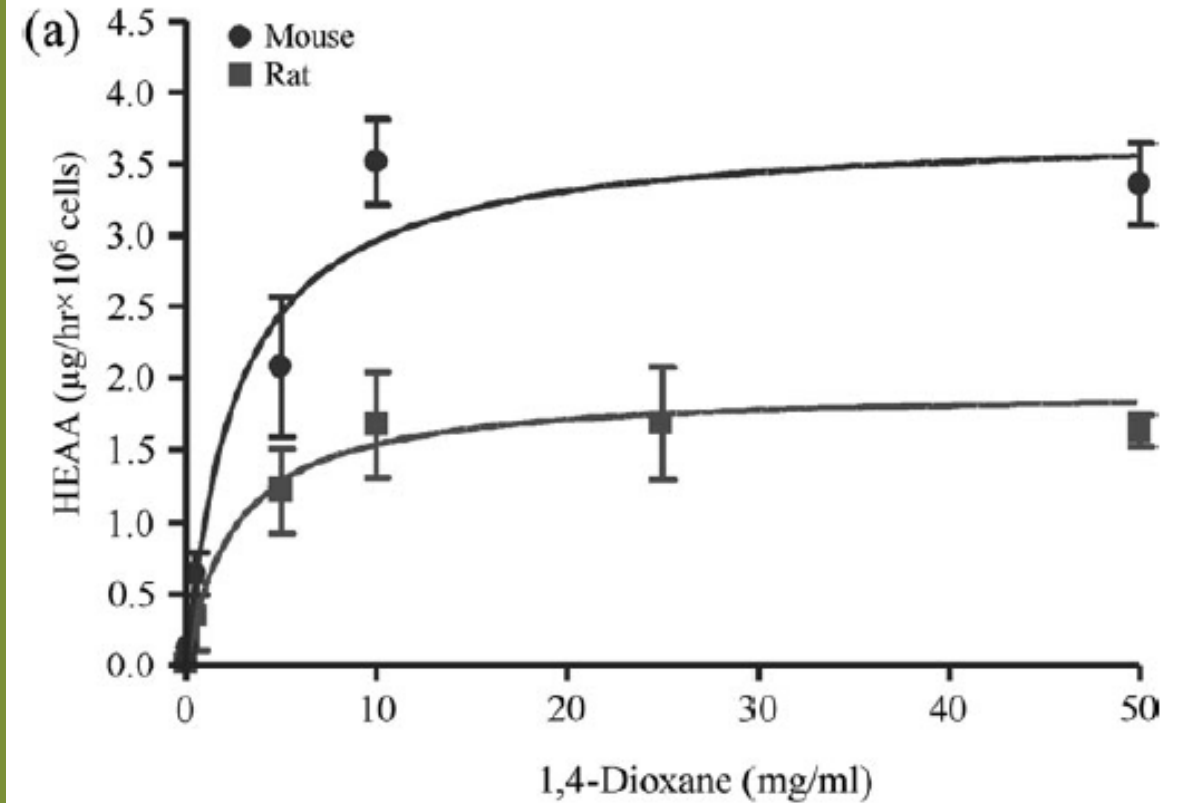
*Reg Tox Pharma* 88:45-55 (2017)

Toxicokinetics characterized

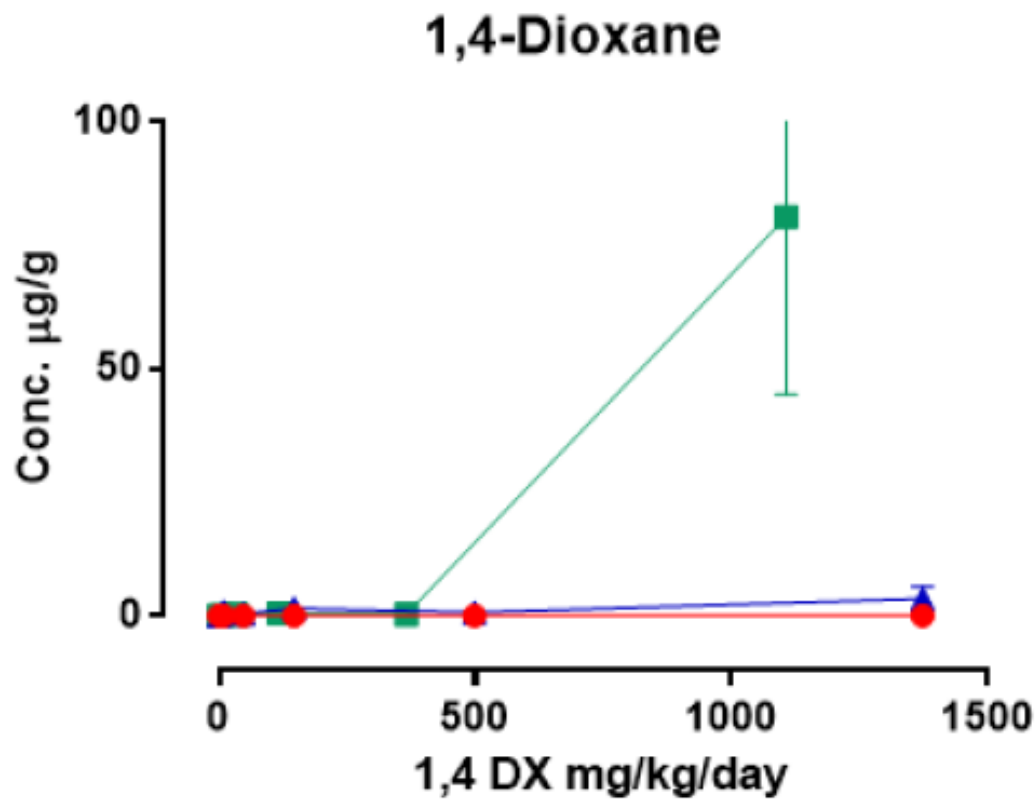
Threshold for metabolism  
identified



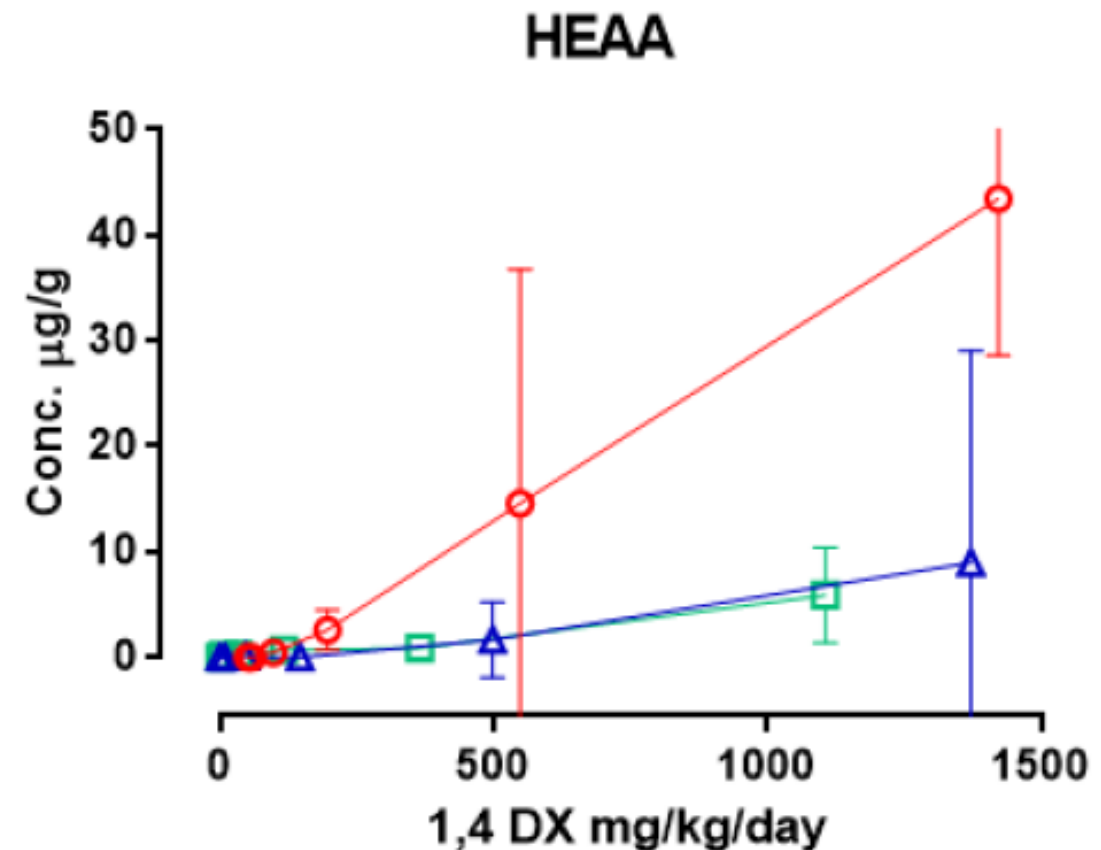
# Characterization of Metabolism - fate of 1,4-DX in rodents



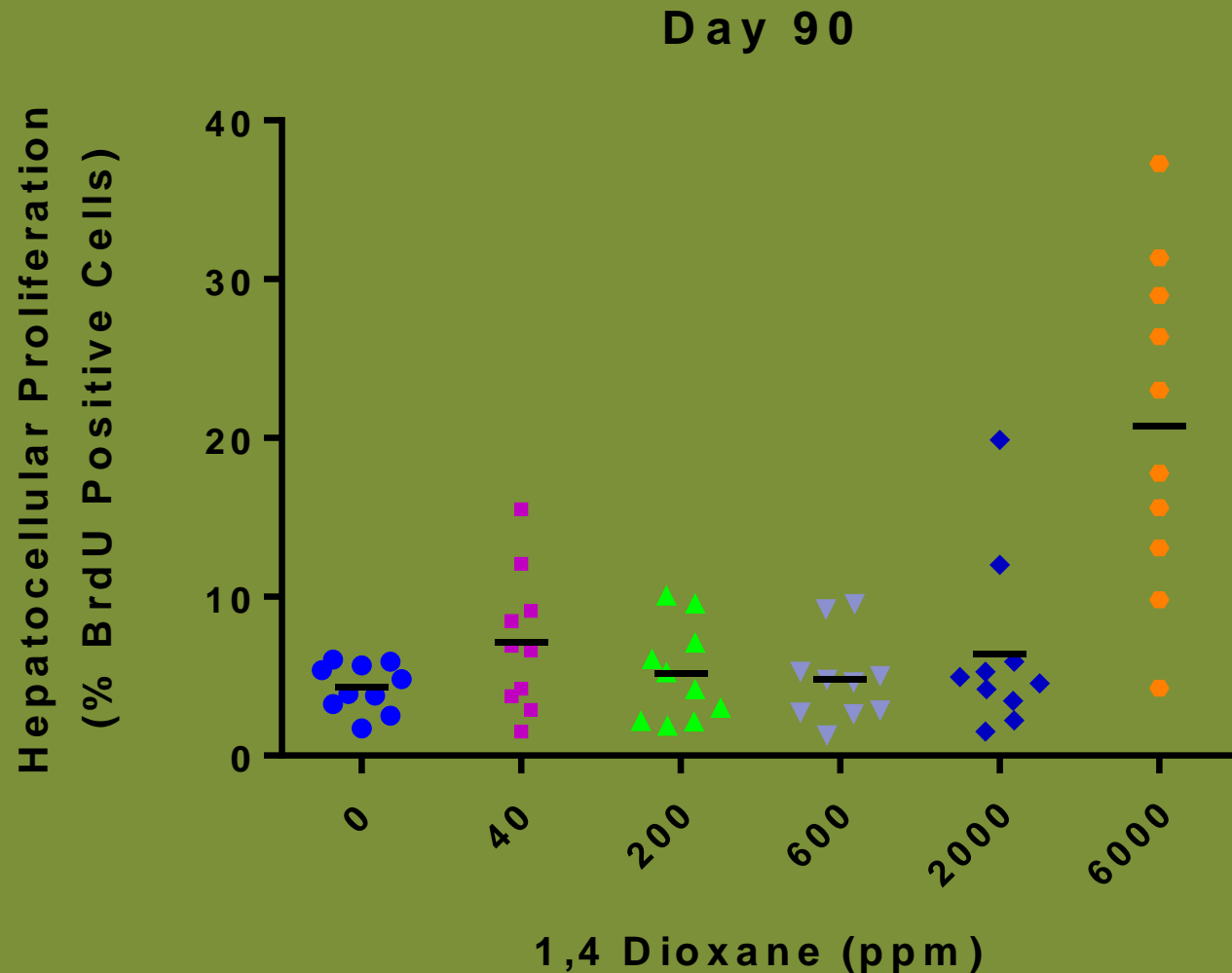
# Characterization of Metabolism - Blood Levels in Female Mice (ACC data)



○ 7 Day  
△ 28 Day  
□ 90 Day



# Proliferative Response in Female Mice (ACC data)

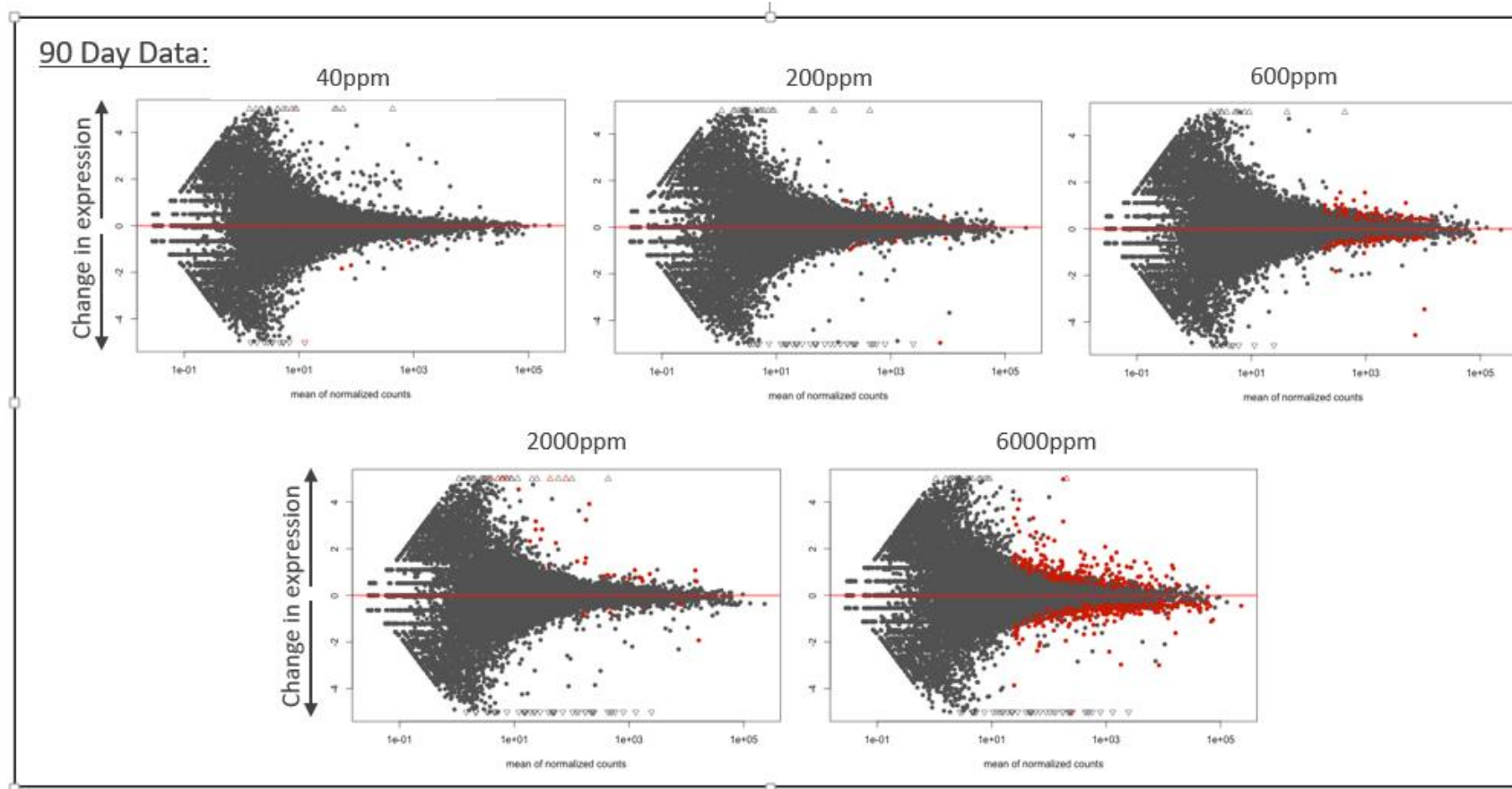


- Gene sets related to proliferation significantly enriched after 90 days at 6000 ppm
  - Regulation of Mitotic Cell Cycle
  - Negative Regulation of Mitotic Cell Cycle
  - Mitotic Cell Cycle Checkpoint
  - Positive Regulation of Mitotic Sister Chromatid Separation
  - Mitotic G1-G1 S Phase
  - M-G1 Transition
  - Cell Cycle Mitotic

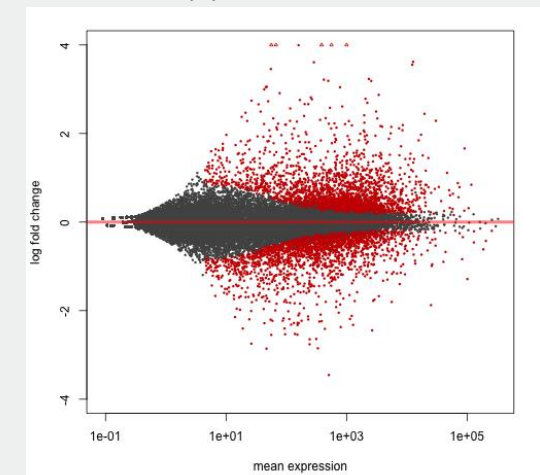


# Differential Gene Expression (ACC data)

- Alterations at the transcriptomic level were minimal, but with a clear threshold demonstrated



For reference: example plot from analysis pipeline manual



# Key Events in the Regenerative MOA for Carcinogenicity

